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ORIGINAL

Etomidate versus ketamine for emergency endotracheal intubation: a randomized clinical trial

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Abstract

Purpose: Etomidate and ketamine are hemodynamically stable induction agents often used to sedate critically ill patients during emergency endotracheal intubation. In 2015, quality improvement data from our hospital suggested a survival benefit at Day 7 from avoidance of etomidate in critically ill patients during emergency intubation. In this clinical trial, we hypothesized that randomization to ketamine instead of etomidate would be associated with Day 7 survival after emergency endotracheal intubation.

Methods: A prospective, randomized, open-label, parallel assignment, single-center clinical trial performed by an anesthesiology-based Airway Team under emergent circumstances at one high-volume medical center in the United States. 801 critically ill patients requiring emergency intubation were randomly assigned 1:1 by computer-generated, pre-randomized sealed envelopes to receive etomidate (0.2–0.3 mg/kg, $n = 400$) or ketamine (1–2 mg/kg, $n = 401$) for sedation prior to intubation. The pre-specified primary endpoint of the trial was Day 7 survival. Secondary endpoints included Day 28 survival.

Results: Of the 801 enrolled patients, 396 were analyzed in the etomidate arm, and 395 in the ketamine arm. Day 7 survival was significantly lower in the etomidate arm than in the ketamine arm (77.3% versus 85.1%, difference − 7.8, 95% confidence interval − 13, − 2.4, $p = 0.005$). Day 28 survival rates for the two groups were not significantly different (etomidate 64.1%, ketamine 66.8%, difference − 2.7, 95% confidence interval − 9.3, 3.9, $p = 0.294$).

Conclusion: While the primary outcome of Day 7 survival was greater in patients randomized to ketamine, there was no significant difference in survival by Day 28.

Keywords: Etomidate, Ketamine, Emergency endotracheal intubation, Anesthetic induction medication, Airway management

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Introduction

Etomidate and ketamine are often used to sedate critically ill patients during emergency endotracheal intubation [1–4]. Both drugs have rapid onset and hemodynamic stability compared to other induction agents [1]. Clinical practice guidelines recommend either agent for emergency endotracheal intubation of patients in shock [5].

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It is not known if one agent is more hemodynamically stable than the other in acute critical illness [1]. Ketased, the largest randomized trial to date of etomidate versus ketamine in critically ill patients ($n=655$), reported no significant difference in the acute hemodynamic effects between the two agents [6]. Conversely, recent observational studies from the National Emergency Airway Registry (NEAR) Database have reported that ketamine may be associated with more-frequent hypotension than etomidate in critically ill patients [1, 7].

The major adverse effect of etomidate is inhibition of 11-beta hydroxylase in the adrenal glands [8]. Recognition of this effect in the 1980s led to recommendations to avoid continuous infusions of etomidate [8, 9]. The use of a single dose of etomidate in critically ill patients has been studied prospectively in eight published randomized trials to date [6, 10–16]. These trials employed a variety of primary endpoints and enrolled 1203 patients collectively. A meta-analysis of available randomized trial data in 2015 found that use of etomidate is associated with a positive Adrenocorticotropic Hormone (ACTH) stimulation test as well as slightly higher Sequential Organ Failure Assessment (SOFA) scores, but no evidence of increased mortality [17]. Other meta-analyses combining clinical trial data with observational and retrospective data have suggested that there is an increased risk of mortality from a single dose of etomidate [18, 19]. Uncertainty about the safety of a single dose of etomidate in critically ill patients has led to robust debate [20–23].

At our hospital most out-of-operating room emergency intubations are performed by a high-volume, procedure-focused "Airway Team" which is anesthesiology-based and siloed from the intensive care unit (ICU) teams. In 2015 we analyzed Quality Improvement (QI) outcomes from our Airway Team from two time periods, July–December 2014, and January–May 2015. Those data (unpublished) revealed that > 50% of patients received etomidate during emergency intubation at our institution. Receipt of etomidate during emergency intubation was associated with − 13% and − 12.3% aggregate Day 7 survival within each time period, respectively, relative to other induction agents.

The aim of the EvK Clinical Trial was to compare clinical outcomes between critically ill adult patients at our hospital who received etomidate versus ketamine for emergency endotracheal intubation. Based on our QI data, our hypothesis was that ketamine would be associated with increased chance of survival at Day 7 in critically ill patients. The pre-specified primary endpoint of the EvK Clinical Trial was survival at Day 7. Primary and secondary outcome data from the EvK Clinical Trial were presented at the American Society of Anesthesiology Annual Meeting on 9–10 October 2021 in San Diego [24].

Take-home message

In this single-center clinical trial, patients randomized to ketamine instead of etomidate had greater survival at Day 7 but not at Day 28 after emergency endotracheal intubation. Further work is needed on this subject.

Methods

Trial design and setting

Etomidate versus Ketamine for Emergency Endotracheal Intubation: A Randomized Clinical Trial (The EvK Clinical Trial, NCT02643381, UTSW IRB STU#022015-023) was a prospective, randomized, parallel-assignment, open-label, single-center trial carried out between 6 June 2016 and 7 September 2020 in an urban, academic, Level-1 Trauma hospital in Dallas by a procedure-focused Airway Team. The Airway Team is managed and staffed by the Department of Anesthesiology and is distinct and siloed from the ICU teams. Members of the Airway Team do not participate in day-to-day management of ICU patients. This trial received contingent Institutional Review Board (IRB) approval on 28 October 2015, and full approval on 30 November 2015. Continuing Reviews were completed and approved on 19 August 2016, 3 August 2017, 26 July 2018, 7 August 2019, and 7 August 2020.

The EvK Clinical Trial received IRB approval to be conducted as an Exception from Informed Consent (EFIC) trial, a specialized type of clinical trial used for studying emergency medical procedures. Critically ill patients are unable to participate in a consent discussion immediately before emergency intubation. In the United States rules for this type of clinical trial are listed in FDA 21 CFR 50.24. Prior to the start of enrollment, we engaged in extensive community consultation and public disclosure activities, essential parts of EFIC clinical trials. These methods have been published previously [25]. We continuously offered "opt-out" alert bracelets through a study website (www.evktrial.org) during the trial, to give individuals in our community an opportunity to formally opt-out of potential enrollment in the trial. Over the course of the trial, we received (and fulfilled) one request for an opt-out bracelet through our website.

Patient selection

We designed the screening and enrollment protocol to fit within the contemporaneous usual-care practices of our Airway Team. The members of our Airway Team were encouraged to consider screening and enrolling patients

whenever clinical circumstances reasonably permitted but were under no obligation to do so. If the members of the Airway Team believed a specific induction agent was indicated for an eligible patient based on individualized usual-care practices, the Airway Team was permitted to screen-out that patient, even if specific exclusion criteria were not technically met.

Formal inclusion criteria included any adult patient 18 years and older in need of emergency endotracheal intubation. Formal exclusion criteria included children (< 18 years), women known to be pregnant, patients previously enrolled in the trial, patients requiring endotracheal intubation without sedative medication such as those in cardiac arrest, those neurologically obtunded, or those requiring awake intubation. We also excluded patients with a known allergy to etomidate or ketamine, and anyone wearing an opt-out bracelet indicating that she/he has formally opted out of the clinical trial. All areas of the hospital were potential enrollment locations.

Randomization procedures

Adult patients requiring emergency intubation were screened and enrolled by our Airway Team immediately prior to intubation using sequentially numbered, opaque, sealed envelopes containing cards that directed the Airway Team to use either etomidate or ketamine as the primary anesthetic, as well as a suggested dose range (etomidate 0.2–0.3 mg/kg intravenous; ketamine 1–2 mg/kg intravenous). Members of the Airway Team were permitted to adjust the doses of induction medications for individual patients as they believed clinically appropriate. The randomization sequence (etomidate versus ketamine) was 1:1, computer-generated, in blocks of eight to ensure balanced groups. The exterior of each envelope was printed with a screening aid which harmonized with the inclusion/exclusion criteria.

Randomization to etomidate or ketamine was a one-time intervention. There were no antecedent or subsequent study interventions, and no masking/blinding of the critical care teams. All subsequent medical or surgical care was at the direction of the treating critical care teams. Following enrollment patients and/or their families were notified of enrollment using a multi-step IRB-approved notification protocol (including up to three attempts at in-person/bedside visit(s) by the study team as well as mailed letters) and were asked to permit or decline data collection. No information was collected from patients who declined data collection, other than internal registration information for our IRB. Data collection occurred only after this notification process was completed.

Airway team practices and techniques

Other than induction medication, all other techniques of intubation were at the discretion of the members of the Airway Team. Our Airway Team is managed and staffed by the Department of Anesthesiology and is distinct and separate from the critical care teams. The Airway Team is a self-sufficient, mobile anesthesia unit which travels to all areas of the hospital with an assortment of basic and advanced airway equipment (traditional laryngoscopes, videolaryngoscopes (both C-MAC® and GlideScope®), fiberoptic intubating bronchoscopes, laryngeal mask airways, adjunctive airway devices, suction equipment) and anesthetic medications (induction agents, neuromuscular blocking agents, vasopressors). An Anesthesia Equipment Technician is part of our Airway Team at all intubations, in addition to the skilled operators performing the intubation.

Our Airway Team routinely uses a bundle of clinical techniques which align with a validated approach to emergency intubation in an ICU setting (Montpellier-Intubation Protocol [26–28]). This includes the routine presence of two or more skilled operators, head-up (20–30 degree) positioning, deliberate pre-oxygenation strategies, routine use of rapid sequence induction with neuromuscular blocking agents, routine use of intubating stylets [29], frequent use of cricoid pressure (Sellick Maneuver), frequent first-pass use of videolaryngoscopy, strict confirmation of all endotracheal intubations by detection of end-tidal CO_2, and prompt treatment of post-intubation hypotension with bolus-dose vasopressors and intravenous fluids.

Trial endpoints

The pre-specified primary endpoint was Day 7 survival. We defined this as the proportions survived on Study Day 7. Randomization occurred on Study Day 1. The primary endpoint was unchanged since initial IRB approval in 2015. This was published on a public registry (www.clinicaltrials.gov/ct2/show/NCT02643381) on December 31, 2015, prior to the start of enrollment. A final Statistical Analysis Plan (SAP) was uploaded to our study website (www.evktrial.org) in August 2020.

Secondary endpoints included proportion survived on Study Day 28, duration of mechanical ventilation, ICU length-of-stay, usage and duration of vasopressor therapy, serial SOFA scores [30, 31] on Day 1–4, and an assessment of a new diagnosis of adrenal insufficiency by the treating critical care teams.

Exploratory endpoints included immediate technical and hemodynamic outcomes of intubation. Immediate technical endpoints included induction drug dose, neuromuscular blocking agent and dose, choice of laryngoscope, number of intubation attempts, and complications

such as major soft-tissue trauma, dental trauma, aspiration events, clinically significant bleeding, or requirement for surgical airway. Immediate hemodynamic outcomes included measurement of blood pressure and heart rate before and after induction as well as acute interventions for hypotension or cardiovascular collapse such as vasopressor bolus, intravenous fluid bolus, or cardiopulmonary resuscitation with chest compressions (CPR). In the final SAP, we added the Vanderbilt Definition of post-induction cardiovascular collapse [32–34] as an additional exploratory endpoint. This definition is (A) new (post-induction) systolic blood pressure < 65 mmHg, and/or (B) immediate need for IV vasopressor bolus or dose escalation, and/or (C) cardiac arrest or death within 1 h. This definition has been used in prior works [32, 33] and was congruent with our preexisting data collection practices related to other exploratory endpoints.

Electronic medical records were assessed by manual review for the presence or absence of a clinical diagnosis of adrenal insufficiency made by the treating critical care teams, regardless of cortisol testing. In the process of assessing each chart for a diagnosis of adrenal insufficiency we gathered supportive data about post-randomization steroid use (hydrocortisone, methylprednisolone, dexamethasone and/or prednisone) and post-randomization cortisol measurements. Those data are included in Electronic Supplementary Material (ESM) 2.

Biostatistics and data collection

The EvK Clinical Trial was designed and powered to have 80% power with 0.05 level of significance to detect a 10% difference in proportions survived at 7-day post endotracheal intubation. Based on retrospective quality improvement data from our hospital, the proportions of patients survived are assumed to be 60% and 70% for the etomidate and ketamine groups, respectively. With these assumptions, $n = 750$ patients (etomidate $n = 375$, ketamine $n = 375$) would be needed to have 80% power. Assuming a 10% dropout rate we received IRB approval to enroll a maximum of $n = 825$ patients. The trial had one pre-planned interim analysis (O'Brien-Flemming futility analysis with pre-planned stopping parameters) at the midway point of enrollment ($n = 375$).

Formal statistical oversight, including completion of the interim analysis, was conducted by a Data Safety and Monitoring Board (DSMB) which included four expert clinicians (AAF, JMcG, DMcD, MJL) who were not involved with day-to-day trial activities, assisted by our study statistician. These individuals did not participate in randomization or enrollment activities, nor did they participate in the Airway Team.

All study data were collected and managed in a customized Research Electronic Data Capture (REDCap) [35] database hosted by UT-Southwestern Medical Center. Primary and secondary endpoints were assessed by manual chart review of ICU flowsheets and progress notes. Use of vasopressors/inotropes was determined by examination of ICU flowsheets, and excluded bolus-dose vasopressors/inotropes that were given in the immediate peri-intubation period of time. Duration of mechanical ventilation, ICU length-of-stay, diagnosis of adrenal insufficiency, and survival endpoints were all assessed by manual chart review of progress notes and ICU flowsheets. Individual components of SOFA scores on Day 1–4 were collected by manual extraction from the Electronic Medical Record (EMR) within four sequential 24-h windows of time which started on the day of randomization. Serial SOFA scores were calculated automatically from these primary data by an algorithm embedded in our database.

Exploratory endpoints were assessed from several distinct data sources which included the short-form anesthetic records generated by the Airway Team, as well as the hand-written "code sheets" generated by independent nurses at each intubation. The code sheets were completed by nurses who are independent of the Airway Team, which is a routine practice at our hospital during emergency intubations. Induction agent and neuromuscular blocking agent were identified on the short-form anesthetic records primarily, secondarily on the hand-written code sheets if documentation was missing from the anesthetic record. Techniques of intubation and number of intubation attempts were extracted from the short-form anesthetic records. Complications were assessed from both the short-form anesthetic records and code sheets. Vital signs pre- and post-intubation were extracted from the nurses' code sheets. Data related to post-induction vasopressor/inotrope bolus or dose escalation, post-induction IV fluid bolus, and post-induction CPR (with chest compressions) were extracted from the nurses' code sheets. Members of the Airway Team other than the Principal Investigator did not have access to the study database during enrollment.

Outcomes were analyzed in an intent-to-treat manner. The null hypothesis of no difference in proportions survived at 7-day post-intubation was tested using a log-rank chi-square test. Kaplan-Meier survival curves were estimated. Results for the primary study aim were summarized as p value and 95% confidence interval for hazard ratio. Chi-square tests, Fisher's exact test, Student's t test and log-rank test were used to test hypotheses related to secondary end-points. All analyses were done with a 0.05 level of significance.

In May 2018, at the mid-way point of the study, a planned interim analysis was performed by the DSMB to assess futility using the O'Brien-Fleming approach.

At that time, the proportions surviving at 7-day post-randomization for the etomidate and ketamine groups were 79.8% and 87.2% respectively, and the DSMB voted to complete enrollment in the trial. Enrollment was suspended in September 2020 by vote of the DSMB because the number of enrolled patients minus the number of withdrawals was substantially greater than 750. In December 2020, the DSMB closed the trial permanently because the number of enrolled minus the number of withdrawals was still substantially greater than 750. Following closure of the trial, the survival data were verified within the EMR by three members of our study team who do not report to the Principal Investigator and who were unaware of group assignments (BF, MCS, LAC).

Results

Trial patients

A total of 801 critically ill patients requiring emergency endotracheal intubation were enrolled by 162 members of our Airway Team between June 6, 2016 and September 7, 2020. The median number of skilled operators present at each enrollment was 2. There was one skilled operator present at 1% of enrollments, two skilled operators present at 91% of enrollments, and three or more skilled operators present at 8% of enrollments. A faculty (consultant) anesthesiologist was present at >99% of enrollments. An Anesthesia Equipment Technician was routinely present at all enrollments.

Figure 1 shows the flow of patients into the trial. Of the 801 randomized patients, 400 were assigned to etomidate and 401 to ketamine. Of the enrolled patients, four in the etomidate arm and three in the ketamine arm received other or unknown induction medications. There were 10 post-enrollment withdrawals (4 assigned to etomidate, 6 assigned to ketamine) which were excluded from all analyses, yielding 396 analyzed in the etomidate arm and 395 in the ketamine arm for the primary and secondary endpoints. There was one significant protocol violation, enrollment of a pediatric patient. Other protocol violations and deviations are listed in ESM 1.

Table 1 shows demographic and baseline characteristics of the 791 analyzed patients. Additional baseline laboratory data are available in ESM 2. Patients were enrolled in all areas of the hospital. The location of patients enrolled physically outside of the ICUs (for example, on the general medical/surgical floors) is categorized in Table 1 by the destination ICU assignment where possible. Sepsis was a common pre-randomization diagnosis among the patients enrolled in this clinical trial. A sizeable number of patients in each group acquired a new diagnosis of sepsis from our ICU clinicians after randomization (Table 1). Most patients enrolled in this trial were treated with intravenous antibiotics (Table 1).

Primary and secondary endpoints

Kaplan-Meier product-moment estimates of proportion survival at Day 7 for etomidate and ketamine groups were 77.3% (90 deaths out of 396) and 85.1% (59 deaths out of 395), respectively. The difference in proportion survived was significantly greater in the ketamine arm of the trial (log-rank p value = 0.005, Fig. 2, Table 2). Patients in the etomidate arm were 1.6 times more likely to die compared to patients in the ketamine arm (hazard ratio = 1.6, 95% confidence interval: 1.2, 2.2). At Day 28, the estimated survival rate for etomidate and ketamine arms were 64.1% (142 deaths out of 396) and 66.8% (131 deaths out of 395). The difference was not statistically significant (log-rank p value = 0.294, Fig. 2, Table 2).

Duration of mechanical ventilation, ICU length-of-stay, and percent vasopressor use and duration were not significantly different between the two arms of the study (Table 2). Analysis of serial SOFA scores on Day 1–4 showed no clinically meaningful differences between the two study arms at any point evaluated (ESM 2). There was no statistically significant difference in the percentage of patients in each group that received a clinical diagnosis of adrenal insufficiency (with or without cortisol testing) (Table 2).

Exploratory outcomes of intubation

Table 3 shows the exploratory acute outcomes of intubation. ESM 2 has supplemental histograms and scatterplot data. Induction drug doses were consistent with the doses recommended in the trial protocol. Most patients received a dose of a neuromuscular blocking agent. There were no obvious imbalances between the two group on neuromuscular blocking agent or dose, laryngoscope choice, number of attempts to intubate, or technical (non-hemodynamic) complications (Table 3).

Blood pressure and heart-rate before and after intubation were not significantly different between the two arms of the study (Table 3 and ESM 2). However, a greater percentage of patients randomized to ketamine received acute hemodynamic support with bolus-dose vasopressors than patients randomized to etomidate. The proportion of patients who experienced post-induction hemodynamic collapse based on the Vanderbilt Definition [32–34] was greater in the ketamine arm than in the etomidate arm (Table 3).

Discussion

In this clinical trial, we found that patients randomized to ketamine had a significantly higher likelihood of Day 7 survival but not Day 28 survival (Table 2, Fig. 2). None of the secondary endpoints were significantly different between the two arms of the trial including duration of mechanical ventilation, ICU length-of-stay, percent usage

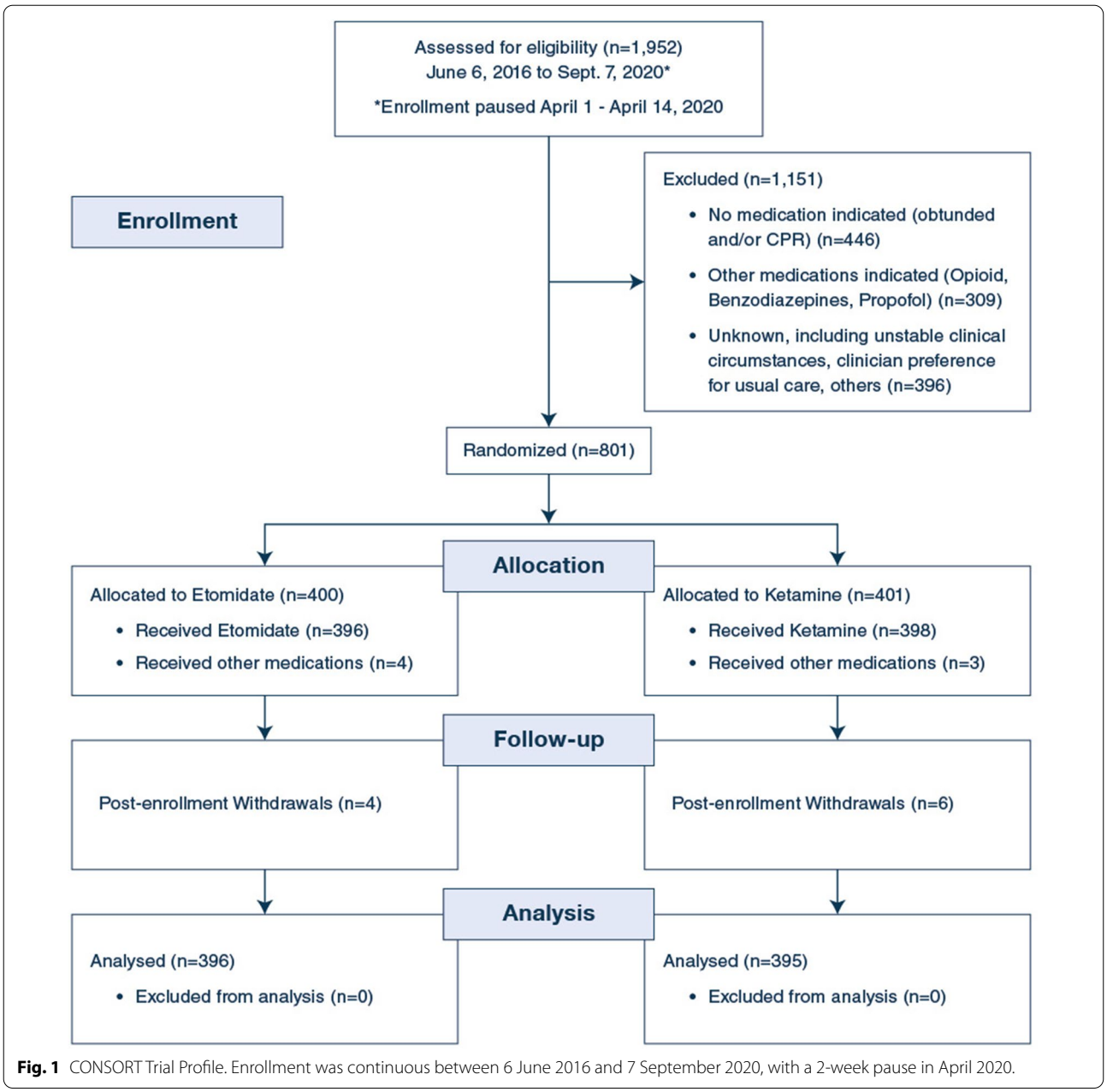
Assessed for eligibility (n=1,952)
June 6, 2016 to Sept. 7, 2020*
*Enrollment paused April 1 - April 14, 2020
Enrollment
Excluded (n=1,151)
• No medication indicated (obtunded and/or CPR) (n=446)
• Other medications indicated (Opioid, Benzodiazepines, Propofol) (n=309)
• Unknown, including unstable clinical circumstances, clinician preference for usual care, others (n=396)
Randomized (n=801)
Allocation
Allocated to Etomidate (n=400)
• Received Etomidate (n=396)
• Received other medications (n=4)
Allocated to Ketamine (n=401)
• Received Ketamine (n=398)
• Received other medications (n=3)
Follow-up
Post-enrollment Withdrawals (n=4)
Post-enrollment Withdrawals (n=6)
Analysis
Analysed (n=396)
• Excluded from analysis (n=0)
Analysed (n=395)
• Excluded from analysis (n=0)

Fig. 1 CONSORT Trial Profile. Enrollment was continuous between 6 June 2016 and 7 September 2020, with a 2-week pause in April 2020.

or duration of vasopressor therapy, serial SOFA scores on Day 1–4, or the percentage of patients with a new diagnosis of adrenal insufficiency (Table 2, ESM 2).

The survival curves in Fig. 2 are statistically different at Day 7 but converge by Day 28. We do not have an explanation for this observation, although there are several possibilities. The early survival gap in Fig. 2 could be artifactual. The gap could be a consequence of unknown or unmeasured conditions or treatments that had a differential short-term but not long-term effect on survival between the two arms of the trial. Or the early survival gap could be a sign of a small but durable long-term survival effect, one which our trial was under-powered to detect. None of these possibilities are excluded by our data. It is difficult to determine the broader implications, if any, of the main findings of the trial because of the convergence of the curves in Fig. 2.

The immediate technical outcomes of intubation were similar between the two arms of the trial (Table 3) and were comparable to technical outcomes reported by recent randomized trials of emergency airway management in an ICU setting [29, 36]. Measurement of heart

Table 1 Baseline characteristics

Variable	Etomidate (*n* = 396)	Ketamine (*n* = 395)
Age, years, mean (SD)	55.8 (15.2)	55.4 (16)
Age, years, median (IQR)	56 (46, 66)	57 (45, 66)
Female gender, *n* (%)	153 (38.6)	150 (38)
Male gender, *n* (%)	243 (61.4)	245 (62)
Race, *n* (%)		
White	250 (63.1)	246 (62.3)
Black	133 (33.6)	122 (30.9)
Other	13 (3.3)	27 (6.8)
Hispanic ethnicity, *n* (%)	141 (35.6)	139 (35.2)
Weight, kg, mean (SD)	84.6 (30.3)	83.9 (29.9)
BMI, kg/m^2, mean (SD)	29.8 (9.9)	29.6 (10.4)
Destination ICU, *n* (%)		
BICU	29 (7.3)	25 (6.3)
MICU	261 (65.9)	286 (72.4)
NICU	24 (6.1)	23 (5.8)
SICU	79 (19.9)	56 (14.2)
Other	3 (0.8)	5 (1.3)
Knaus chronic health status score[a], *n* (%)		
Category A	78 (19.7)	63 (15.9)
Category B	99 (25)	108 (27.3)
Category C	162 (40.9)	161 (40.8)
Category D	57 (14.4)	63 (15.9)
Reason for intubation, *n* (%)		
Shock	189 (47.7)	174 (44.1)
Acute respiratory failure	175 (44.2)	191 (48.4)
Neurological	27 (6.8)	27 (6.8)
Other	5 (1.3)	3 (0.8)
Vital signs, mean (SD)		
SBP mmHg	120.7 (32.2)	120.3 (29.5)
DBP mmHg	72.7 (23.1)	74.2 (21.6)
MAP mmHg	88.7 (24.2)	89.5 (22.3)
HR beats per minute	112.9 (24.1)	114.7 (23.4)
Temperature, °C, mean (SD)	36.8 (1.6)	36.8 (1.5)
O_2 saturation, %, mean (SD)	95.8 (5.5)	96.1 (5)
Diagnosis of sepsis (pre-randomization)	136 (34.3)	136 (34.4)
Diagnosis of Sepsis (pre- or post-randomization)	204 (51.5)	196 (49.6)
Peri-intubation intravenous antibiotic therapies[b]	360 (90.9)	358 (90.6)
Acute injury, *n* (%)		
Burn	30 (7.6)	25 (6.3)
Trauma	24 (6.1)	31 (7.8)
None	342 (86.4)	339 (85.8)

Data are presented as mean (SD) or number (%) unless otherwise indicated. Additional baseline characteristics are available in ESM 2

BMI body mass index, *BICU* Burn ICU, *MICU* medical ICU, *NICU* neurological ICU, *SICU* surgical ICU

[a] Knaus Chronic Health Score Category A – Previous good health with no functional limitations, Category B – Mild to moderate limitation of activity because of a chronic medical problem, Category C – Chronic disease producing serious but not incapacitating limitation of activity, Category D – Severe restriction of activity due to disease including people incapacitated or institutionalized because of illness

[b] Peri-intubation intravenous antibiotic therapies refers to repeated doses of intravenous antibiotic therapy on any Day 1–4. Prophylactic intraoperative antibiotic dosing was not included in this definition

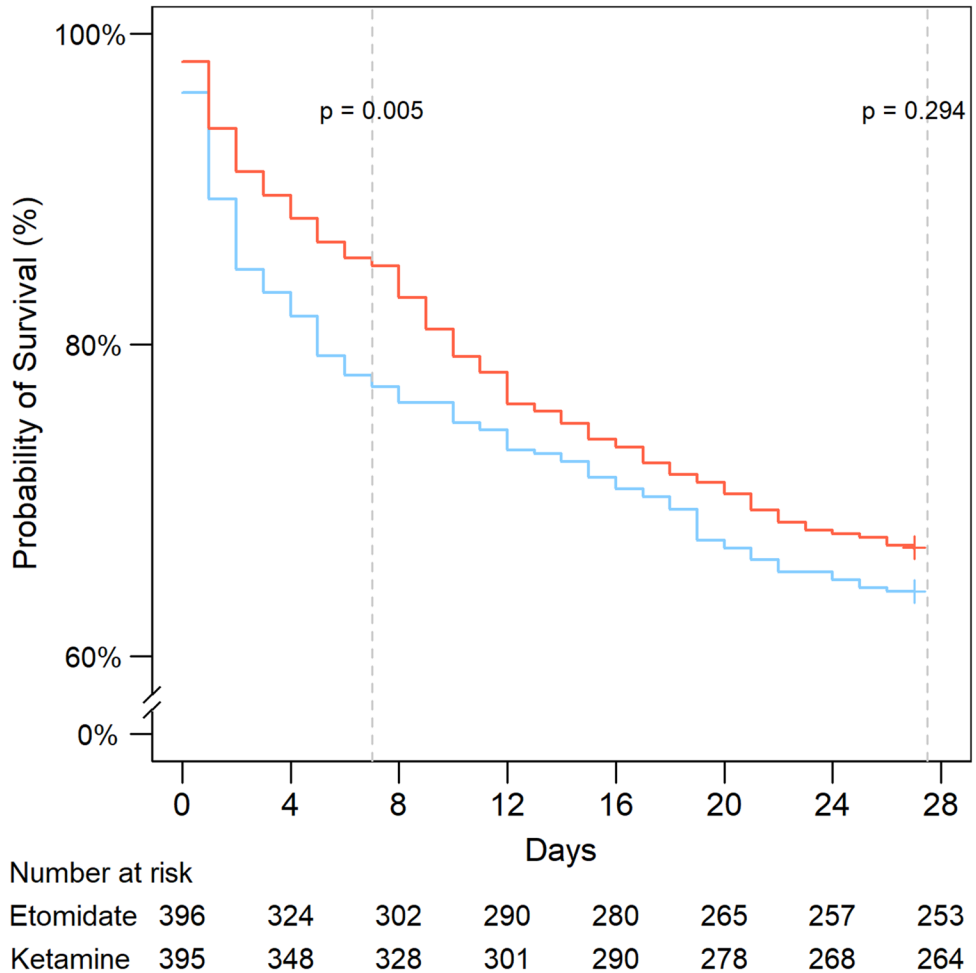

Fig. 2 Kaplan-Meier curves comparing patients randomized to receive etomidate (blue) or ketamine (red) during emergency endotracheal intubation. Day 7 Survival was significantly greater in patients randomized to ketamine ($p = 0.005$). Day 28 Survival was not significantly different between the two groups ($p = 0.294$).

Table 2 Primary and secondary outcomes

Variable	Etomidate ($n = 396$)	Ketamine ($n = 395$)	Difference (95% confidence interval)	p value
Receiving vasopressor or inotrope infusion(s), *n* (%)[a]	235 (59.3)	213 (53.9)	5.4 (− 1.5, 12.3)	0.124
Duration of vasopressor or inotrope infusion(s) (days), median (IQR)	1 (0, 3)	1 (0, 3)	0 (0, 0)	0.498
Duration of mechanical ventilation, median (IQR)	5 (3, 9)	5 (3, 10)	0 (− 1, 0)	0.446
ICU length-of-stay, median (IQR)	8 (4, 16)	9 (5, 14)	− 1 (− 1, 0)	0.302
Diagnosis of adrenal insufficiency, n (%)	11 (2.8)	4 (1)	1.8 (− 0.1, 3.7)	0.115
Day 7 survival, *n* (%)	306 (77.3)	336 (85.1)	− 7.8 (− 13, − 2.4)	0.005
Day 28 survival, *n* (%)	254 (64.1)	264 (66.8)	− 2.7 (− 9.3, 3.9)	0.294

Data are presented as mean (SD), number (%) unless otherwise indicated

[a] Includes receipt of any continuous vasopressor or inotrope infusion (epinephrine, phenylephrine, norepinephrine, dopamine, dobutamine, vasopressin, milrinone) at any point on Day 1-4 which was documented on the ICU flowsheets. This did not include isolated bolus doses of vasopressors (or inotropes) administered during or immediately after intubation

Table 3 Exploratory outcomes of intubation

Variable	Etomidate ($n = 396$)	Ketamine ($n = 395$)	Difference (95% confidence interval)
Induction drug dose, mg, mean (SD)	16.4 (6.1)	91.8 (40.9)	–
Induction drug dose, mg/kg, mean (SD)	0.2 (0.1)	1.2 (0.5)	–
Induction drug dose, mg/kg, median (IQR)	0.2 (0.15, 0.25)	1.1 (0.8, 1.5)	–
Neuromuscular blocking agent, *n* (%)[a]	394 (99.5)	394 (99.7)	− 0.3 (− 1.1, 0.6)
Rocuronium	316 (79.8)	327 (82.8)	− 3 (− 8.4, 2.4)
Succinylcholine	78 (19.7)	64 (16.2)	3.5 (− 1.8, 8.8)
Other	0 (0)	3 (0.8)	− 0.8 (− 1.6, 0.1)
Neuromuscular blocking agent dose, mean (SD)			
Rocuronium, mg/kg	1.2 (0.4)	1.2 (0.4)	0 (− 0.1, 0.1)
Succinylcholine, mg/kg	1.8 (0.5)	1.8 (0.6)	− 0.1 (− 0.3, 0.1)
Laryngoscope Used, *n* (%)[b]			
Direct laryngoscopy-Macintosh blade	198 (50.8)	206 (53.2)	− 2.5 (− 9.5, 4.6)
Video laryngoscopy-any blade	176 (45.1)	169 (43.7)	1.5 (− 5.5, 8.4)
Direct laryngoscopy-Miller blade	14 (3.6)	11 (2.8)	0.7 (− 1.7, 3.2)
Other	2 (0.5)	1 (0.3)	0.3 (− 0.6, 1.1)
Number of intubation attempts, *n* (%)[c]			
1 (successfully intubated)	357 (91.3)	355 (91.3)	0 (− 3.9, 4)
2 (successfully intubated)	29 (7.4)	26 (6.7)	0.7 (− 2.9, 4.3)
3+ (successfully intubated)	4 (1)	5 (1.3)	− 0.3 (− 1.8, 1.2)
Surgical airway	1 (0.3)	3 (0.8)	− 0.5 (− 1.5, 0.5)
Any technical (non-hemodynamic) complication, *n* (%)[d]	23 (5.8)	19 (4.8)	1 (− 2.1, 4.1)
Post-induction blood pressure and heart rate, mean (SD)			
SBP mmHg	118.3 (39.3)	112.8 (38.7)	5.5 (− 0.6, 11.6)
DBP mmHg	70.7 (24.8)	69 (24.9)	1.7 (− 2.2, 5.6)
MAP mmHg	86.5 (28)	83.6 (28.1)	3 (− 1.4, 7.3)
HR beats per minute	121.1 (27)	124.2 (23.4)	− 3.1 (− 8.5, 2.2)
Delta SBP mmHg[e]	− 2.6 (30.8)	− 7.3 (32.7)	4.7 (− 0.3, 9.7)
Delta DBP mmHg[e]	− 2.3 (22.5)	− 4.7 (23.5)	2.5 (− 1.1, 6.1)
Delta MAP mmHg[e]	− 2.4 (23.2)	− 5.6 (24.8)	3.2 (− 0.6, 7)
Delta HR beats per minute[e]	7.6 (17.1)	8.9 (17.4)	− 1.3 (− 5, 2.4)
Post-induction vasopressor bolus, *n* (%)[f]	65 (18.8)	92 (26)	− 7.1 (− 13, − 1)
Post-induction IV fluid bolus, *n* (%) [f]	50 (14.5)	63 (17.8)	− 3.3 (− 8.8, 2.1)
Post-induction CPR, *n* (%)[f]	13 (3.8)	18 (5.1)	− 1.3 (− 4.4, 1.7)
Post-induction cardiovascular collapse, Vanderbilt Definition, *n* (%)[g]	69 (17.4)	99 (25.1)	− 7.6 (− 13, − 2)

Data are presented as mean (SD), number (%) unless otherwise indicated

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial blood pressure, *HR* heart rate, *CPR* cardiopulmonary resuscitation

[a] Neuromuscular blocking agent was missing for two patients in Etomidate and one patient in Ketamine group

[b] Information on laryngoscope used was missing for six patients in Etomidate and eight patients in Ketamine group. The Airway Team has both GlideScope® and C-MAC® videolaryngoscope blades in various geometric configurations available as standard equipment

[c] The number of attempts to intubate is missing for five patients in the etomidate group and six patients in the ketamine group, all of whom were successfully intubated using non-surgical techniques according to chart documentation

[d] Technical (non-hemodynamic) complications included major soft-tissue trauma, dental trauma, aspiration events, clinically significant bleeding or requirement for surgical airway

[e] Delta refers to post-induction value minus pre-induction value

[f] Data regarding acute vasopressor bolus, IV fluid bolus and immediate post-induction CPR (with chest compressions) were taken from the nurses' code sheets, which were unavailable for 51 patients randomized to etomidate and 41 randomized to ketamine

[g] The Vanderbilt Definition of post-induction cardiovascular collapse [32–34] is defined as a new post-induction systolic blood pressure < 65 mmHg and/or immediate need for vasopressor bolus or dose escalation and/or cardiac arrest or death within 1 hour

rate and blood pressure immediately before and after induction did not reveal a substantial difference between groups, although the large standard deviations and small absolute differences suggest it is unlikely our trial was large enough to reliably detect a difference between groups at these exploratory endpoints (Table 3, ESM 2). We did observe that randomization to ketamine was associated with more-frequent administration of post-induction rescue therapy with vasopressors, and with a greater incidence of post-induction cardiovascular collapse (Table 3). Given the amount of missing data and similarity of post-induction heart rate, blood pressure and change in blood pressure, these differences are of uncertain clinical significance and should be viewed as hypothesis generating.

Both etomidate and ketamine are considered hemodynamically stable induction agents. There is not an established consensus in published literature regarding the relative hemodynamic stability of one compared to the other [1]. Ketased, the largest randomized trial to date of etomidate versus ketamine in critically ill patients, did not report an acute hemodynamic difference between the two agents [6]. Two small observational studies in a pre-hospital setting did not find a significant difference in the acute hemodynamic effects of etomidate versus ketamine [37, 38]. A 4-year interrupted time series (ITS) analysis of an institutional change-in-practice from etomidate to ketamine during emergency intubation of trauma patients did not find a difference in the frequency of peri-intubation cardiac arrest [39].

Conversely, recent large-scale, multi-center observational studies from the National Emergency Airway Registry (NEAR) Database reported a greater incidence of post-induction hypotension during emergency intubation with ketamine compared to etomidate [1, 7]. Investigators from the NEAR Database also reported the need for more acute post-induction rescue vasopressor therapy in patients who had received ketamine [1]. Observational studies of ketamine in pre-hospital [40], emergency department (ED) [41], and mixed ED and ICU [2] settings have found that induction doses of ketamine may be associated with post-induction hypotension, particularly among patients in shock [40]. Although not conclusive, we believe our exploratory data (Table 3) generally align with these observational studies [1, 2, 7, 40, 41], and suggest the need for additional research into the acute effects of etomidate versus ketamine.

Limitations

There are several important limitations of our study. The EvK Clinical Trial was a single-center trial, and the generalizability of our findings is unknown. The trial was conducted at a medical center with a specialized, high-volume Airway Team which is additive to the pre-existing ICU teams. Our Airway Team routinely uses advanced techniques and practices which align with validated approaches to emergency intubation in an ICU setting [26–28]. Not all hospitals have these resources or employ these techniques, and this structure itself could limit the generalizability of our findings. We believe this limitation is particularly relevant to mitigation of acute post-induction hemodynamic instability that was present in both groups (Table 3).

The extent of data collection for the exploratory outcomes (Table 3) was limited in scope. We did not assess the proportion of patients experiencing cardiovascular collapse prior to induction of anesthesia, nor did we quantitively assess preexisting intravenous fluid and vasopressor therapies. Similarly, we did not quantitively assess the cumulative rescue vasopressor dose or the cumulative intravenous fluid dose immediately after intubation. These important limitations reinforce the need to view the outcomes in Table 3 as hypothesis-generating.

In the design phase of the trial, we considered ways of potentially masking (blinding) the critical care teams to induction medication. After extensive discussions with hospital and community stakeholders, we were unable to arrive at a satisfactory plan for masking. As a result, we conducted the trial entirely open-label. This decision could have impacted outcomes to an uncertain but potentially large magnitude. Outcomes related to the diagnosis of adrenal insufficiency are likely susceptible to confounding by knowledge of group. For example, perhaps our critical care teams were more inclined to make a diagnosis of adrenal insufficiency or perform treatments for suspected adrenal insufficiency in patients who had received etomidate.

We used a pragmatic approach to screening and enrollment in this trial, one which prioritized patient safety over other matters. Our clinicians were allowed to screen-out patients when they believed a specific induction medication was indicated for a specific patient, thereby forgoing trial enrollment and defaulting to individualized usual-care practices. This likely had the effect of biasing trial enrollment toward patients for whom our clinicians genuinely believed either etomidate or ketamine would be a good choice. We do not know what other biases this enrollment practice may have introduced. The net result was a relatively high screen-failure rate (Fig. 1), but also a well-balanced enrollment profile (Table 1, ESM 2) in which most patients received their assigned induction medication (Fig. 1).

Day 7 survival is an unconventional primary endpoint for a randomized trial of critically ill patients. We chose this endpoint based on empirical observations of our QI data, and because we wanted to place the primary

endpoint relatively close in time to the randomization event. We know of no precedent for this endpoint in other trials. There are some significant disadvantages to having used Day 7 survival as the primary endpoint, besides the fact that it is unconventional. The relevance, if any, of Day 7 survival to long-term outcomes in acute critical illness is uncertain. Given the statistical convergence of the survival curves beyond Day 7, any hypothetical long-term benefit from avoiding etomidate needs to be carefully weighed against the risk of acute hemodynamic instability that could be caused by alternative agents. Further research is needed on this subject.

Conclusion

While the primary outcome of Day 7 survival was greater in patients randomized to ketamine, there was no significant difference in survival by Day 28.

Supplementary Information

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OA-Enrollment, manuscript drafting. BJB-Enrollment, manuscript drafting. CGE-Enrollment, manuscript drafting. BF-Study design, CRNA coordination, enrollment, manuscript drafting. PEF-Study design, data management and informatics, enrollment, manuscript drafting. IG-Study design, enrollment, manuscript drafting. LWL-Study design, enrollment, resident coordination, manuscript drafting. GM-Study PI, study design, enrollment, manuscript drafting. AM-Study Statistician, study design, statistical calculations, manuscript drafting. TSM-Study design, enrollment, manuscript drafting. DN-Study design, enrollment, manuscript drafting. BOO-Study design, enrollment, manuscript drafting. CAR-Study design, enrollment, manuscript drafting. MNS-Enrollment, manuscript drafting. JWS-Enrollment, manuscript drafting. MCS-Study design, CRNA coordination, enrollment, manuscript drafting. DT-Enrollment, manuscript drafting.

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Availability of data and materials

Our IRB approval does not include provisions for sharing individual patient-level data.

Code availability

Not applicable.

Declarations

Conflicts of interest

CAR: Receives compensation for serving on the Medical Advisory Board for Vyaire. The other coauthors declare no conflicts-of-interest, and no competing interests.

Ethical approval

This trial (NCT02643381, UTSW IRB STU022015-023) received contingent Institutional Review Board (IRB) approval on 28 October 2015, and full approval on 30 November 2015. Continuing Reviews were completed and approved on 19 August 2016, 3 August 2017, 26 July 2018, 7 August 2019, and 7 August 2020.

Consent to participate
This clinical trial received IRB approval to be conducted as an Exception-from-Informed-Consent trial under emergency clinical circumstances.

Consent for publication
Enrolled patients and/or their survivors were notified of enrollment and given an opportunity to opt-out of data collection and inclusion.

PI data statement
The study PI (GM) is responsible for the veracity of all study data and all aspects of this manuscript.

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